Overview of the CGMP Requirements Relevant to Cell Therapies

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Summary

- Only addressing those HCT/Ps that also meet the definition of a drug and a biological product – not addressing drug or device products or combination products
- Discussion of the statutes and the regulations that would apply and be applied to these products in the investigational and approved state.

NOTE

- For products that meet the definition of a drug under section 201(g) of the FDCA, the CGMP regulations apply regardless of application status. This is also true for products that also meet the definition of a biological product under section 351(i) of the PHSA.

CGMP?

- Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FDCA) states that a drug shall be deemed adulterated if “the methods used in, or the facilities and controls used for, its manufacturing, processing, packing, or holding do not conform to or are not operated or administered in conformity with

CGMP?

- **..current good manufacturing practice** to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets quality and purity characteristics, which it purports or is represented to possess."

Current Good Manufacturing Practice (CGMP)?

- Regulations at 21 CFR Parts 210 and 211
- Applicable to preparation of drug products for administration to humans and animals, including clinical trials
- GMPs cover manufacturing, controls, testing and documentation
- CGMP - the “C” means current - GMPs are minimal standards.

Status of CGMP Regulations

- 21 CFR 210.1(a)
- …..the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

Drug substance or intermediate production

- What is the difference between a drug product and a drug substance?
- Production of the drug product refers to the preparation of the finished dosage form, so processes leading up to that point produce intermediates or drug substances that are not specifically covered under Parts 210-211
- HOWEVER, the statutory GMP is applied, similar expectations.

Public Health Service Act

- Section 351(a)(2)(B)
- Biologics license application shall be approved on the basis of a demonstration that-
- The biological product ..subject to the application is safe, pure and potent.
- The facility in which the biological product is manufactured, processed, packed or held meets the standards designed to assure that the biological product continues to be safe, pure and potent.

Applicable Licensing Regulations

- 21 CFR 601.2(d)
- Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product subject to this section shall include but not be limited to the good manufacturing practice requirements set forth in **parts 210, 211**, **600**, 606, and 820 of this chapter.

Applicable Licensing Regulations

- 21 CFR 601.20(a)
- Examination--compliance with requirements. A biologics license application shall be approved only upon examination of the product and upon a determination that the product complies with the standards established in the biologics license application and the requirements prescribed in the regulations in this chapter including but not limited to the good manufacturing practice requirements set forth in **parts 210, 211, 600**, 606, and 820 of this chapter.

What about Part 1271?

- 21 CFR 1271.150(a)

This subpart D (GTPs) and subpart C (Donor Eligibility) of this part set forth current good tissue practice (CGTP) requirements. You must follow CGTP requirements to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps (e.g., by ensuring that the HCT/Ps do not contain communicable disease agents, that they are not contaminated, and that they do not become contaminated during manufacturing).

What about Part 1271?

- 1271.150(a)
- Communicable diseases include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents.
- CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution.

Conforming amendments

- 21 CFR 1271.150(d)

Compliance with parts 210, 211, and 820 of this chapter. With respect to HCT/Ps that are drugs (**subject to review** under an application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act or under a biological product license application under section 351 of the Public Health Service Act) or that are devices (subject to premarket review or notification under the device provisions of the act or under a biological product license application under section 351 of the Public Health Service Act), the procedures contained in this subpart and in subpart C of this part and the current good manufacturing

practice regulations in parts 210 and 211 of this chapter and the quality system regulations in part 820 of this chapter supplement, and do not supersede, each other unless the regulations explicitly provide otherwise.

In the event that a regulation in part 1271 of this chapter is in conflict with a requirement in parts 210, 211, or 820 of this chapter, the regulations more specifically applicable to the product in question will supersede the more general.

What does this mean?

- **Due to the broader scope of these regulations, most of the CGMP regulations under Parts 210 and 211 would be applicable for HCT/Ps that are not regulated solely under section 361 of the PHSA and meet the definition of drugs in the FDCA and biologics in the PHSA. Other regulations, outside of CGMP would also applicable, depending on whether the HCT/P is under IND or has an approved BLA.**

Broader in Scope?

- Address safety, purity, potency, and quality of the drug product;
- Potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect the given result

Broader in Scope?

- CGTPs address transmission of communicable disease, which is one issue related to safety; however, other safety concerns may be present due to, for example, the purity or quality of the drug product
- Therefore, for the most part, the CGMPs would be applied and the CGTPs subsumed under the broader CGMP requirements
- Compliance with these CGMP requirements would mean compliance with CGTP requirements

What other regulations may be applied?

- Prior to licensure:
- 21 CFR Part 50 – Informed consent
- 21 CFR Part 54 – Financial disclosure for clinical investigators
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 58 – Non-clinical studies (GLP)
- 21 CFR Part 312 - INDs

What other regulations would be applicable?

- Reporting requirements in 21 CFR Part 600 would apply after a product is licensed
  - 21 CFR 600.80 for Adverse Event Reporting
  - 21 CFR 600.14 for Biological Product Deviation Reporting.
- In addition, the other licensing and biologics standards in Parts 600-680, as applicable.
- Some of labeling regulations in Parts 201 and 202 would apply after licensure.

Would any GTPs apply?

- YES, again, all apply but most subsumed by the broader GMPs. Which GTPs would be applicable and must be followed?:
  - Subpart C: Donor eligibility requirements are unique to the GTPs and would be applied
  - Information on Donor Eligibility would also be contained in an IND or BLA.

Compliance with applicable requirements

- 1271.150(c) – Before entering into a contract, agreement or other arrangement…you must ensure that the other establishment complies with applicable CGTP requirements.
- If you become aware of information suggesting that the establishment is not in compliance with such requirements:
  - Take reasonable steps to ensure compliance with requirements
  - Terminate your contract, agreement or other arrangement

Exemptions and alternatives

- 21 CFR 1271.155
  - Those relating to Subpart C; Donor Eligibility
  - May be considered for those relating to provisions in Subpart D, taking into account the corresponding CGMP
  - 1271.155 (b) – (g) describe the procedures for requesting an exemption or alternative; criteria for granting such a request; operating under and properly documenting once granted and issuance in a public health emergency.

Quality Program

- 21 CFR 1271.160(b)(2)
- Having procedures for sharing information pertaining to possible contamination or potential for transmission of communicable disease with other establishments:
  - Known to have recovered from same donor
  - Known to have performed manufacturing steps with respect to the same HCT/P

- 21 CFR 1271.160(c)
  - Audits – as defined in 1271.10(gg) for core GTPs;
  - Relating to communicable disease transmission
  - Required for core GTPs such as donor eligibility
  - Could be performed more broadly for the corresponding CGMPs to satisfy the requirement ;

What about the other GTP Quality Program requirements?

- Limited to procedures governing core GTPs
- The GMPs provide for a Quality Control Unit that has broad responsibility
- This responsibility is described under 21 CFR 211.22
- Also interspersed throughout the GMP regulations

Quality Control Unit
21 CFR 211.22

- Responsibility and authority to approve/reject all components, in-process materials, packaging, labeling and drug products and authority to review records to assure no errors have occurred and if occur; fully investigated; including contract operations.
- Responsibility to approve/reject procedures/specifications impacting on identity, strength, quality, and purity of the drug product
- Adequate laboratory facilities for testing
- Responsibilities and procedures in writing

Additionally

- 21 CFR 211.100
  - Production and process controls procedures (process validation), including changes ..reviewed and approved by the QCU.
- 21 CFR 211.160
  - Establishment of specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including changes to any…reviewed and approved by the QCU

Additionally

- 21 CFR 211.192 – Production Record Review
  - All drug product production and control records…shall be reviewed by the QCU to determine compliance with all established, approved, written procedures before a batch is released or distributed. Any discrepancies must be thoroughly investigated .

Additionally

- 21 CFR 211.198 - Complaint Files
  - Written procedures established and followed, including provisions for review by the QCU of any complaint related to drug product failures; need for investigation; need to evaluate whether represents and adverse drug experience and, if so, reported properly

GTPs that would be applicable

- Processing and process controls
- 21 CFR 1271.220(b)
  - Pooling – Human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.
- 21 CFR 1271.220(d) Dura mater (not likely)
- GMPs applicable to other production and processing controls: process validation, in-process testing, change control, as apply to identity, strength, quality and purity

Examples of GTP vs. GMP

- 21 CFR 1271.265 – some distinctions from or complement to 211 requirements:
- (a) Receipt procedures for HCT/Ps; requires evaluation of incoming HCT/Ps with respect to presence of microorganisms, damage and contamination. Decision to accept, reject or quarantine.
- 21 CFR 211.84(a) requires procedures in sufficient detail for the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components

- Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the drug product.
- Very broad in scope; covers incoming HCT/P for further manufacture as well as components used in manufacture (i.e. supplies and reagents under 21 CFR 1271.

- 21 CFR 1271.265 (b) Predistribution shipment
  - Distinctive in GTPs as specifically addresses shipment of HCT/Ps prior to release for distribution.
  - Would be applicable

- 21 CFR 1271.265(c) Availability for distribution
  - (1) covered by 211.22, 211.165, 211.167, 211.192
  - (2) specific to review of donor eligibility; so would be applicable
  - (3) covered under 211.192
  - (4) specific to packaging and shipping of HCT/Ps; so would be applicable

- 21 CFR 1271.265(c) – Availability for distribution
  - (e) – requirements for procedures for documentation of release and distribution covered under GMPs
  - (f) – return to inventory covered under 211.204; returned drug products

Records

- 21 CFR 1271.270
  - (a) – (c) – covered under GMPs, e.g. 211.180, 211.188
  - (d) requires retention of records for 10 years; so would be applicable
  - (e) – records of all contracts and agreements; not required under GMP; so would be applicable

Tracking

- 1271.290
- Tracking – (a) – (g) – distinctive to HCT/Ps in tracking requirements, distinctive codes; relating to donor ; so would be applicable
- 211.196 CGMP requirement for distribution records is not as specific. Requires record contain, for example, name and strength of product, description of dosage form, and lot or control number

CGMP Sections:

- ✓ Organization and personnel
- ✓ Building and facilities
- ✓ Equipment
- ✓ Control of Components
- ✓ Production and Process Controls
- ✓ Packaging and Labeling Control
- ✓ Holding and Distribution

CGMP Sections:

- Laboratory Controls
- Records and Reports
- Returned and Salvaged Drug Products

Are CGMPs applicable while under IND?

- YES;
- 21 CFR 312.23(a)(7)
- Must assure proper identification, quality, purity and strength of the investigational product
- Amount of information will vary with the phase of the investigation, the proposed duration, the dosage form and amount of information otherwise available

Are CGMPs applicable while under IND?

- Examples:
- FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses.
- Final specifications are not expected until the end of the investigational process

Conclusion

- The CGTPs and the CGMPs apply to HCT/Ps that are also drug and biological products
- CGMPs are applicable, for the most part, as these regulations cover safety, purity, potency, and quality of the drug product; which would include transmission of communicable disease agents
- Other regulations would be applied depending on whether the HCT/P is under IND or has an approved BLA.